Decision Memo for External Counterpulsation (ECP) Therapy (CAG-00002R2)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is not adequate to conclude that external counterpulsation therapy is reasonable and necessary for the treatment of:

- Canadian Cardiovascular Society Classification (CCSC) II angina
- Heart Failure
  - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 35%
  - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 40%
  - New York Heart Association Class IV heart failure
  - Acute heart failure
- Cardiogenic shock
- Acute myocardial infarction

Current coverage as described in Section 20.20 of the Medicare National Coverage Determination (NCD) manual will remain in effect.

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Decision Memo

TO: Administrative File: CAG-00002R2
External Counterpulsation Therapy

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SUBJECT: Coverage Decision Memorandum for External Counterpulsation Therapy
DATE: March 20, 2006

I. Decision

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Current coverage as described in Section 20.20 of the Medicare National Coverage Determination (NCD) manual will remain in effect.

II. Background

External counterpulsation is a non-invasive procedure that can be used to treat various conditions on an outpatient basis. For this decision the requestor is seeking extended coverage for certain cardiac conditions (as the device is also used for other medical conditions that are not cardiac conditions), where the intended clinical result of external counterpulsation (ECP) is to increase the heart's oxygen supply while decreasing its oxygen demand. ECP systems consist of inflatable pneumatic-compressive cuffs, valves, and compressors synchronized with an electrocardiograph (ECG). These devices inflate and deflate a series of pneumatic-compressive cuffs enclosing the lower extremities. Treatment occurs on a padded table in which three sets of electronically controlled inflation and deflation valves are located. These valves connect to adjustable cuffs that wrap firmly around the patient's calves, lower thighs, and upper thighs including the buttocks. External pressure is applied to the patient through inflation of the cuffs. In early diastole, pressure is applied sequentially from the lower legs to the lower and upper thighs to displace a volume of blood back to the heart. Then, when the left ventricle contracts and the cuffs deflate, aortic pressure is reduced as the volume of blood upstream of the cuffs fills the lower extremities. Pressure settings can be varied to effect certain blood pressure changes during treatment, with the blood pressure monitored by finger plethysmography. Treatments are usually given in one-hour sessions once or twice a day and a full course of treatment is typically defined as 35 hours.

Though studies investigating the mechanism of action date to the 1960s, the exact physiologic mechanism remains unclear.

III. History of Medicare Coverage

Prior to July 1, 1999, a national non-coverage policy for all uses of ECP was delineated in Section 35-74 of the Medicare Coverage Issues Manual (CIM).

In April of 1999, after review of a published randomized study, the MUST-EECP trial, Section 35-74 was amended to remove the national non-coverage policy previously in place and allow coverage for this procedure under certain circumstances. Coverage for ECP was provided only for patients who have been diagnosed with disabling angina (Class III or Class IV, Canadian Cardiovascular Society Classification or equivalent classification) and who, in the opinion of a cardiologist or cardiothoracic surgeon, are not readily amenable to surgical intervention. This change became effective July 1, 1999.

Also, effective July 1, 1999, the name for this procedure was changed to "Enhanced External Counterpulsation (EECP)." The Centers for Medicare and Medicaid Services (CMS), formerly the Health Care Financing Administration (HCFA), based this change on the information presented by Vasomedical, Inc., which referred to its device as the "Enhanced External Counterpulsation (EECP®) System" and the name of the therapy as "Enhanced External Counterpulsation." Additionally, the majority of the medical literature regarding this procedure refers to EECP, and the MUST-EECP study was conducted using devices supplied by Vasomedical, Inc.

Soon after this decision, another manufacturer, Cardiomedics Inc., presented information about the EECP terminology used in the CIM. Cardiomedics Inc. objected to the use of this trademarked term, suggesting that CMS alter the language of the instruction so that coverage of this treatment would not exclude manufacturers other than Vasomedical. CMS accepted Cardiomedic's formal request to reconsider this decision on July 9, 1999.

On October 6, 1999, CMS accepted a request for reconsideration of the entire EECP policy submitted on behalf of the Medicare Contractor Medical Director New Technology Workgroup, which believed that there was not sufficient evidence to permit coverage. The two requests were combined. After review, the positive coverage decision remained in effect and the CIM was amended to remove any reference to the trademarked term EECP and to remove language which had limited coverage of this therapy to specific ECP systems.

On April 11, 2001, CMS accepted a request from the Circulator Boot Corporation to reconsider the ECP policy. In its request, the Circulator Boot Corporation pointed out that the original evidence considered for this (ECP) policy did not support CMS' statement that "other uses of this device and similar devices remain non-covered." This request was based on the contention that CMS had misinterpreted the ECP evidence to include non-coverage of other end diastolic pneumatic compression devices cleared by the FDA for non-cardiac conditions. Furthermore, the Circulator Boot Corporation pointed out that CIM 35-74 explicitly defines ECP as a non-invasive outpatient treatment for coronary artery disease refractory to medical and or surgical therapy, with no specific mention of coverage or non-coverage for other non-cardiac indications. At the core of its request, the Circulator Boot Corporation contended that the Circulator Boot was designed for the treatment of vascular diseases of the lower extremity and therefore differs significantly from ECP devices that are designed for the treatment of cardiac conditions.

According to the 510(k) summary information included in the FDA's clearance letter dated August 14, 1997, the Circulator Boot was found to be equivalent to the original Circulator Boot, the Jobst Extremity Pump, and the Cardiassist ECP device. Note that devices with similar FDA classifications do not necessarily imply that the clinical indications for the devices are the same.

After a review of this reconsideration request, CMS concluded that the policy set forth in CIM section 35-74 should be limited to ECP devices intended for the treatment of cardiac conditions. Other non-cardiac conditions in which end diastolic pneumatic compression devices may be considered for coverage are not considered under this policy. Therefore, Medicare contractors would continue to have discretionary authority in making reasonable and necessary coverage determinations related to other end diastolic pneumatic compression devices not related to this policy or included in any other section of the CIM. CIM 35-74 was amended to indicate that this policy pertains **only** to ECP devices intended for the treatment of certain cardiac conditions.

Current Request

On June 20, 2005, CMS accepted a request from Vasomedical Inc. to reconsider the ECP policy. In this reconsideration, Vasomedical Inc. is requesting that CMS expand coverage of ECP to include treatment of patients with Canadian Cardiovascular Society Classification (CCSC) II angina and for use in patients with New York Heart Association (NYHA) Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 35%.

On June 23, 2005, CMS also received a request from Cardiomedics to reconsider the ECP policy. Cardiomedics requests expansion of coverage to include 1) treatment of congestive heart failure, to include NYHA Class II, III with a left ventricular ejection fraction (LVEF) $\leq$ 40%, and acute heart failure; 2) treatment of stable angina to include CCSC II angina; 3) treatment of acute myocardial infarction; 4) treatment of cardiogenic shock. On September 15, 2005, Cardiomedics amended their request to include NYHA Class IV heart failure.

CMS is evaluating both requests in this analysis.

On December 14, 2005 Cardiomedics, during a meeting with CMS, requested to amend their request and withdraw the request for coverage for acute congestive heart failure and to include coverage for acute myocardial infarction where percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) is not available. Due to the lateness of this request and the inclusion of both congestive heart failure and acute myocardial infarction in our analysis, CMS does not feel it is necessary to amend the analysis at this time.

On January 20, 2006 Vasomedical, during a meeting with CMS, submitted subgroup data from the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH) trial for consideration in this analysis.

Benefit Categories

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. §1812 (Scope of Part A); §1832 (Scope of Part B); §1861(s) (Definitions of Medical and Other Health Services). External counterpulsation therapy is eligible for coverage under §1861(s)(1), Physicians Services.

IV. Timeline of Recent Activities

May 31, 2005	Vasomedical Inc. submitted a cover letter and supporting documentation requesting that CMS expand coverage indications for external counterpulsation therapy.
June 20, 2005	CMS opened the National Coverage Determination (NCD) process based on Vasomedical's request. Tracking sheet was posted to web site. Public comment period for 30 days begins.
June 29, 2005	Tracking sheet amended to include Cardiomedics' request. Public comment period extended to July 29.
July 29, 2005	Public comment period closed.
August 29, 2005	Meeting with Vasomedical.
September 15, 2005	Cardiomedics submitted letter to amend their request.
December 14, 2005	Meeting with Cardiomedics.
December 20, 2005	CMS posted the proposed decision memorandum on the CMS web site and invited public comment.
January 17, 2006	Meeting with Vasomedical.
January 20, 2006	Public comment period closed.

V. FDA Status

The FDA approved the CardiAssist™ ECP system for the treatment of angina, acute myocardial infarction and cardiogenic shock under a 510(k) submission in 1980

(http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm?ID=27812)

(last accessed March 13, 2006). Since then, additional ECP devices have been cleared by the FDA for use in treating stable or unstable angina pectoris, acute myocardial infarction, cardiogenic shock, and congestive heart failure.

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comment sometimes cites the published clinical evidence and gives CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

Ideally, the goal of external counterpulsation treatment should be to decrease morbidity and improve mortality by reducing ischemia through favorably impacting myocardial oxygen supply and demand, and consequently reducing symptoms and improving functional capacity. Traditional outcomes (whether or not a patient benefits from the medical care provided) that reliably affect morbidity and mortality are outcomes of interest to CMS. Other measures of interest can also include quality of life and related to this, patient symptoms. Rigorous research design leads to the most convincing and dependable outcome results. A randomized trial best demonstrates the effectiveness of an intervention, serving to protect against selection bias (choosing subjects with certain attributes that may unduly influence the outcome) in the assignment process, and assuring that the degree of baseline comparability for an unobserved variable is the same as for the observed variable. Additionally, to determine if a treatment leads to the subsequent outcome, comparison groups (controls) are necessary. Case study or case series lacks a comparison with an untreated group or with a group receiving some other treatment. Evidence about whether the treatment directly causes the subsequent outcome (or whether there is something else that actually causes the outcome) cannot be discerned.

Clinical outcomes including functional classification of angina pectoris, Canadian Cardiovascular Society Classification (CCSC), daily anginal counts, and nitroglycerin use are most often reported in ECP studies. While CCS class may be considered a measure of functional capacity, it is assessed by the physician based in part on patient reports. While improvement in angina is important, angina (pain) is subjective and is also subject to the phenomenon of regression to the mean (level of perceived pain has a tendency to naturally fluctuate about a mean value, which is the average of the level of pain). It is known that the perception of pain varies from individual to individual, without knowing why this fact is so. As an extreme example, some patients have silent heart disease, and we do not know why they lack pain but have obvious disease. Conversely, other patients have chest pain that is identical to angina, but no reason can be found for the pain when diagnostic studies are performed. Some investigators believe that various factors influence the perception of pain, such as age, sex, and psychological and psychosocial factors, for example. The threshold for pain can also vary within the same person based on environmental and psychosocial factors. Therefore, measuring symptom reduction may not be the same thing as measuring ischemia reduction.

While CCSC is a standard for grading angina in patients with chronic stable angina, the relationship between CCSC and the severity of coronary artery disease (objectively measured by coronary angiography) is not clear. A recent article suggests that the Canadian Cardiovascular Society Classification of exercise angina is not a reliable surrogate for the severity of coronary artery disease, as there has been shown generally little correlation between exercise angina class and angiographic findings (the only positive findings were that class I patients had less left main disease than class IV, $p = 0.02$, and class IV patients had fewer normal coronary angiograms than class I, $p = 0.001$) (Sangareddi, Chockalingam et al. 2004). It is for these reasons that CCSC, daily anginal counts, and nitroglycerin use alone are not sufficient outcomes for determination of evidence of benefit. In some studies of ECP, cardiovascular stress testing has also been done pre and post treatment. This type of diagnostic testing attempts to elicit cardiovascular abnormalities that are not present at rest to help determine the adequacy of cardiac function for risk or prognostic stratification. There are several stress tests with a variety of variables that can be measured. As with any diagnostic testing, it is important to be able to understand what the results of the test mean. Cardiovascular stress testing can be physiological stress by exercise testing that uses treadmill or bicycle exercise and electrocardiographic and blood pressure monitoring, or pharmacological stress which commonly includes the use of imaging modalities (such as radionuclide imaging and echocardiography). The American Heart Association has produced a guideline for clinical exercise testing laboratories (AHA Guidelines Clinical Exercise Testing Laboratories), which recommends that exercise testing protocols be chosen based on the limitations of the individual, with the desired testing end point reached within 8 to 12 minutes of testing. It further states:

"The demographic data, date of test, and protocol used should be clearly identifiable. The report should include the peak work rate achieved by the patient in METs or VO_2, peak heart rate and blood pressure, and any abnormal signs or symptoms that occurred during or after the test. The ECG data should consist of rest, abnormal exercise changes, and return to baseline. Occurrence of arrhythmias must be noted as well. If ischemia was demonstrated by ECG changes, the time and double product at which the changes initially occurred should be specified. If gas exchange measurements were made, peak oxygen uptake, ventilatory threshold (if achieved), and level of effort should be reported."

For interpretation of an exercise test, the above noted information is recommended. It is important to note abnormalities in exercise capacity, and systolic blood pressure, and heart rate responses to exercise. An important prognostic marker identified in exercise testing is maximum exercise capacity, which is influenced by left ventricular dysfunction. The relationship of exercise capacity and left ventricular function is not without other contributing factors. Exercise capacity is affected by age, general physical conditioning, comorbidities, and psychological state (ACC/AHA 2002 Guideline Update for exercise testing). Several measures can be used as markers of exercise capacity, including maximum exercise duration, maximum MET level achieved, maximum work-load achieved, maximum heart rate, chronotropic incompetence, and double product (rate times pressure) (ACC/AHA 2002 Guideline Update for exercise testing; Gobel, Nordstrom et al. 1978). When exercise testing is being interpreted, it is important that exercise capacity be taken into account. The translation of exercise duration or workload into METs (oxygen uptake expressed in multiples of basal oxygen uptake, 3.5 O_2 mL/kg per minute) provides a common measure of performance regardless of the type of exercise test or protocol used. Importantly, the guideline mentions that risk stratification with an exercise test does not occur in isolation. Exercise testing for risk stratification must be viewed in the context of the patient's other known risk factors (ACC/AHA 2002 Guideline Update for exercise testing).
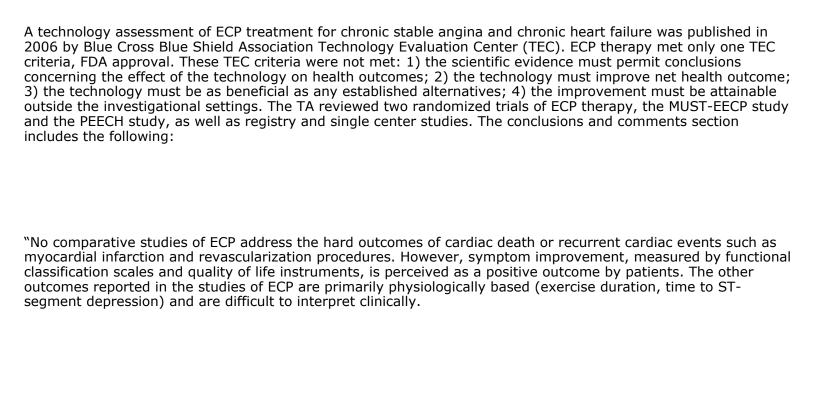
One of the premises of ECP treatment is that effective diastolic augmentation (DA) (the increase of arterial blood pressure and retrograde aortic blood flow during diastole) is an important treatment parameter, as this has been hypothesized to be the main mechanism of effect by some (Suresh, Simandl et al. 1998). To quantify DA, blood pressure changes are monitored by finger plethysmography. Two ratios are computed, using the systolic and diastolic peak pressures or the area under the systolic and diastolic curve. Ratios greater than one indicate that diastolic pressures are greater than systolic pressures. It has been suggested that for optimal hemodynamic effects the DA should be in the range of 1.5 to 2.0 (Suresh, Simandl et al. 1998; Stys, Lawson et al. 2001). While the DA ratio is commonly measured, it has not been clearly correlated with decreased morbidity or mortality, or with improvement in symptoms or quality of life. Given current knowledge, diastolic augmentation is not a sufficient outcome to determine the adequacy of the evidence.

Factors that reliably affect morbidity and mortality are often heavily weighted outcome measures for CMS's analysis of the evidence for a national coverage determination. Morbidity measures of interest include adverse events associated with treatment, subsequent clinical events including illness exacerbation, and hospitalizations and procedures for the condition under study and related conditions. When reporting either morbidity or mortality, it is important to consider potential confounding factors, such as severity of illness and co-morbidities.

Other issues of importance are long-term outcomes and generalizability to the Medicare population.

The outcome relationship to treatment effect is evaluated with the thoughtful application of statistical tools. The goal of most statistical analysis is to form valid conclusions about a population that are based upon information obtained from a sample of that population. A variety of methods exist for analysis. The choice of an appropriate method depends on the purpose of the research as well as the types of variables under investigation (Kleinbaum, Kupper et al. 1988). Data analysis should have a rational for choosing a particular method of analysis (Kleinbaum, Kupper et al. 1988). Additionally, as Kleinbaum, et al., state, "The finding of a "statistically significant" association in a particular study (no matter how well done) does not establish a causal relationship" (Kleinbaum, Kupper et al. 1988). Further, statistical significance should be viewed in the context of clinical significance, for even though a variable may be found to be statistically significant, it may lack clinical significance.

B. Discussion of evidence

1. Questions:

The development of an assessment in support of Medicare coverage decisions is based on the same general question for almost all requests: "Is the evidence sufficient to conclude that the application of the technology under study will improve health outcomes for Medicare patients?" For this NCD, the question of interest is:

Is the evidence sufficient to conclude that the Medicare population will have health benefits for the following conditions as a result of treatment with external counterpulsation therapy?

- Canadian Cardiovascular Society Classification (CCSC) II angina
- Heart Failure - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 35%
  - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 40%
  - New York Heart Association Class IV heart failure
  - Acute heart failure
- Cardiogenic shock
- Acute myocardial infarction

2. External Technology Assessment

No external technology assessment (TA) was commissioned by CMS, however an external TA was identified during the comment period that had been recently published on the topic of ECP.

A technology assessment of ECP treatment for chronic stable angina and chronic heart failure was published in 2006 by Blue Cross Blue Shield Association Technology Evaluation Center (TEC). ECP therapy met only one TEC criteria, FDA approval. These TEC criteria were not met: 1) the scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; 2) the technology must improve net health outcome; 3) the technology must be as beneficial as any established alternatives; 4) the improvement must be attainable outside the investigational settings. The TA reviewed two randomized trials of ECP therapy, the MUST-EECP study and the PEECH study, as well as registry and single center studies. The conclusions and comments section includes the following:

"No comparative studies of ECP address the hard outcomes of cardiac death or recurrent cardiac events such as myocardial infarction and revascularization procedures. However, symptom improvement, measured by functional classification scales and quality of life instruments, is perceived as a positive outcome by patients. The other outcomes reported in the studies of ECP are primarily physiologically based (exercise duration, time to ST-segment depression) and are difficult to interpret clinically.

Although the results of the randomized trial of ECP in angina are consistent with observational studies, the trial does not provide convincing evidence of the efficacy ECP treatment. This trial found statistically significant results in 1 of 4 primary outcomes; treatment extended the time to ST-segment depression by 37 seconds. There was no significant difference between treatment groups in the change in exercise duration from baseline to the post-treatment period ($p<0.31$). In addition, there were no statistically significant differences between groups with respect to angina counts ($p<0.09$) or nitroglycerin usage ($p>0.1$). The single-arm case series and multicenter registry studies provide interesting starting points for research questions that need to be addressed with comparative trials.

The evidence supporting the role of ECP as an effective treatment for heart failure is lacking in both quantity and quality. A single, unpublished controlled trial was mostly inconclusive. It found statistically improved, but modest, changes in exercise duration, and improved functional classification, but not in quality of life or peak oxygen uptake. Registry studies for heart failure use angina outcomes and contribute little to the body of evidence. The single-arm study indicates that patients respond with some improvements, but the lack of a comparison arm precludes inference about the true effects of therapy. Treatment durability has yet to be addressed with long-term studies."

A detailed analysis is provided in the report at http://www.bcbs.com/tec/vol20/20_12.html.

3. Internal Technology Assessment

Vasomedical and Cardiomedics initially provided 17 articles to review for this coverage determination (2 randomized controlled trials, 12 case series reports, 1 trial design, 1 editorial and 1 review). On September 29, Vasomedical provided one previously published article (review) and several other draft articles (one of which was published in the interim) and an abstract. On September 30, Cardiomedics provided a draft article. On January 20, 2006, Vasomedical submitted unpublished subgroup data from the PEECH trial. CMS conducted an independent literature review. Pub Med was searched using combinations of the following terms: enhanced external counterpulsation; external counterpulsation. Google was used for a search using these terms: external counterpulsation; external counterpulsation assessment. No other randomized controlled trials were found. Forty-four other articles were found that included case series (including registry data) and reviews.

Much of the case series data comes from the International EECP Patient Registry (IEPR), which is used to track acute and long-term outcomes for consecutive patients treated for chronic angina. The IEPR began in January 1998 and enrolls patients from > 100 centers in the United States and other countries. The criteria for entry are that the patient give informed consent and have $\geq$ 1 hour of EECP treatment for chronic angina. There are approximately 7,500 patients in the registry.

Evidence Summary

Indication 1: Stable Angina

Most of the published studies concern patients with stable angina. As no separate studies on Class II angina have been published, stable angina will be discussed.

Randomized Controlled Trial Study Design

One published randomized controlled trial for angina, the MUST-EECP trial (Arora, Chou et al. 1999), has been reported to date.

In this trial, participants were randomized and blinded. Medical staff applying the treatment were not blinded. The study had multiple exclusionary criteria:

- MI or CABG in the preceding three months,
- cardiac catheterization in the preceding two weeks,
- unstable angina,
- overt congestive heart failure or a left ventricular ejection fraction $\leq$ 30%,
- significant valvular heart disease, blood pressure > 180/100 mm Hg,
- permanent pacemaker or implantable defibrillator,
- non-bypassed left main stenosis greater than 50%,
- severe symptomatic peripheral vascular disease,
- history of varicosities,
- deep vein thrombosis,
- phlebitis or stasis ulcer,
- bleeding diathesis,
- warfarin use with International Normalized Ratio > 2.0,
- atrial fibrillation or frequent ventricular premature beats that would interfere with EECP triggering or baseline electrocardiographic abnormalities that would interfere with interpretation of exercise electrocardiogram,
- subjects unable to undergo treadmill testing, and
- subjects enrolled in a cardiac rehabilitation program or in another research program.

Patients had symptoms consistent with Canadian Cardiovascular Society Classification angina levels I, II, and III. Control was a sham pressure of 70 mm Hg versus the treatment pressure of 300 mm Hg. There were 72 patients in the active ECP group, with 59 completing the trial. Complete data were not available for the 59 who completed the trial as patient numbers differed for the various outcomes. In the sham ECP group, 67 were randomized and 65 completed the trial. Again, patient numbers varied for the outcomes, with only 56 being included in the exercise time to ST-segment depression from each group. It is not clear if the patients who were excluded from analysis are equivalent to those who were included. The end points were:

1. Exercise duration:
Exercise duration was defined as elapsed time from the initiation of exercise to the beginning of the recovery period as read from the tracing of the exercise treadmill test (ETT). The baseline ETT used either a standard or a modified Bruce protocol and was performed within four weeks of treatment initiation. For the follow-up ETT, "a post-treatment ETT was performed" without details. Baseline and post-treatment ETT were performed by blinded personnel.

2. Exercise treadmill time to $\geq$ 1 mm ST-segment depression:
Time to ST-segment depression was defined as the elapsed time from initiation of exercise to the occurrence of horizontal or down-sloping ST-segment depression $\geq$ 1 mm, 80 ms after the J point, persisting for at least three consecutive beats. As above, baseline ETT used a standard or a modified Bruce protocol. For the follow-up ETT, "a posttreatment ETT was performed" without details.

3. Average daily anginal attack count:

The average frequency of angina episodes per day (angina counts) was computed by dividing the total number of angina episodes reported at three successive treatment sessions by the number of days on which the sessions took place. The first three sessions were considered the baseline period. The difference in angina counts between baseline and at end-treatment were calculated as a percentage change for each patient in the active- and inactive - ECP groups and were then classified categorically.

4. Nitroglycerin usage:
The analysis of average usage of on-demand nitroglycerin tablets per day was accomplished similarly to the analysis of angina counts, but without categorization (reason not given).

Table 1. Study Endpoint Results					
	Treatment Group		Control Group		p
	Baseline	Post-Rx	Baseline	Post-Rx	
Exercise Duration (sec)	426 ± 20	470 ± 20	432 ± 22	464 ± 22	> 0.3
Time to ≥ 1-mm ST-segment depression (sec)	337 ± 18	379 ± 18	326 ± 21	330 ± 20	= 0.01
Mean change in angina counts	0.76 ± 0.15	0.55 ± 0.27	0.76 ± 0.13	0.77 ± 0.2	< 0.09
Mean change in nitroglycerin usage	0.47 ± 0.13	0.19 ± 0.07	0.51 ± 0.15	0.45 ± 0.19	> 0.1

Exercise duration was 426 ± 20 seconds at baseline and 470 ± 20 seconds post-treatment in the treatment group and 432 ± 22 seconds at baseline and 464 ± 22 seconds post-treatment in the control group, with no statistical significance between groups when the group mean increase is compared (see Table 1). Time to $\geq$ 1-mm ST-segment depression was 337 ± 18 seconds at baseline and 379 ± 18 seconds post-treatment in the treatment group and 326 ± 21 seconds at baseline and 330 ± 20 seconds post-treatment in the control group, with statistical significance between groups when the group mean increase is compared (difference of 49 seconds between groups). The difference between groups in the change in angina counts from baseline to post-treatment was not statistically different. The authors then chose to examine angina counts categorically, grouped by percentage improvement or worsening. This categorical outcome did show a p value of < 0.05. The difference between groups in change in nitroglycerin usage from baseline to post-treatment was not statistically significant. In the treatment group, 54.9% (39 of 71) had an adverse experience, while 25.8% (17 of 66) in the sham treatment group had an adverse experience. Adverse experiences that were reported as non-device related (15 in the sham group, 33 in the treatment group) included other chest pain (3 in sham group, 7 in the treatment group), A/V arrhythmia (3 in the sham group, 9 in the treatment group), and respiratory (2 in the sham group, 4 in the treatment group). Adverse experiences that were device related (10 in the sham group and 37 in the treatment group) included skin abrasion, bruise, and blister (2 in the sham group and 13 in the treatment group) and pain (legs, back) (7 in the sham group, 20 in the treatment group).

Seventy-one of the original MUST-EECP patients (54% follow-up) provided health-related quality of life (QOL) information through a mailed questionnaire at 12 months post-treatment (Arora, Chou et al. 2002). Information was collected at baseline before treatment, at the end of treatment, and one year following the end of treatment. Interestingly, both treatment and control groups had improvement in baseline to end of treatment, with the differences between the two groups reported as being statistically significant only for one of the 4 selected parameters. Baseline to 1-year follow-up comparison shows statistical significance between treatment and control groups in bodily pain, social functioning and cardiac specific health and functioning. Baseline data for QOL scores of treatment and control were not provided. Change from baseline to end of treatment and change in baseline to 1 year following end of treatment for the group as a whole was presented. The values at end of treatment or 1 year follow-up were absent. The sample size in this study was set by follow up from the previous trial, not by the power to detect difference. Data were not correlated with the previous data from exercise testing or anginal symptoms. The decrease in anginal episodes reported at the end of active treatment was not reported for the one year outcome.

Case Series Study Design

Extended Prognosis
A 2000 study evaluated the extended prognosis (4 to 7 years) after treatment with external counterpulsation in 33 non-randomized patients with angina (Lawson, Hui et al. 2000). Patients were all treated with ECP (35-36 hours, pressures not listed) and had a radionuclide stress perfusion imaging, both pre and post-treatment. On the basis of imaging improvement after treatment, patients were divided into groups of either responders or nonresponders. The responder group had 26 patients, with 7 in the nonresponder group. The differences in the nonresponders versus the responders were not clear other than 43% of the nonresponders had diabetes, versus 12% of responders, and 100% had multivessel disease, versus 68% of responders. Follow-up treatment decisions were not uniform, but were made by the patient and physician and between group differences are not reported. Post-treatment, anginal symptoms decreased in all patients. Radionuclide stress tests (performed to the same cardiac work load and double product pre and post ECP treatment) demonstrated improvement in perfusion defects in 26 of 33 patients (responders). Stress perfusion defects in the remaining seven patients were unchanged post treatment (nonresponders). A decrease in antianginal medication use was seen in 31% of the responders and in 43% of the nonresponders (p = NS). Over the subsequent course of follow-up, mortality or a major adverse cardiac event (MACE) occurred in 6 of 7 patients in the nonresponder group, and in 6 of 26 patients in the responder group (p < 0.01). Nonresponders had higher major adverse cardiac events. Although patients were followed between 4 to 7 years, it was not clear what determined the follow-up time other than occurrence of outcomes of interest, death or MACE.

A 2005 case series study examined the predictors of benefit in angina one year after therapy and compared initial responders to nonresponders, as defined by those patients with a reduction of at least one CCS angina class after ECP (responders) and those not showing reduction in angina (nonresponders) (Lawson, Hui et al. 2005). From a series of 2,007 patients completing at least 30 hours of ECP, 82.7% were classified as responders. At one year 35.4% of initial nonresponders and 70.6% of responders remained improved by at least one angina class and free of major adverse cardiovascular events (it was not clear if those who were excluded, including those who did not finish treatment, differed from those included in the study). The study listed multivariate predictors of 1-year benefit as initial response to treatment and baseline angina class compared with class IV (odds ratios; class I 2.1, 95% CI 0.93-4.81; class II 0.62, 95% CI 0.43-0.87; class III 0.80, 95% CI 0.62-1.01). In essence, Class I responded better than IV (no statistical significance), class II responded worse that class IV, as did class III (no statistical significance); thus demonstrating no simple trend from a large series of patients. When comparing adverse outcomes, the nonresponders had higher rates of death, MI, CABG, PCI, CABG or PCI, and MACE. Nevertheless the authors concluded, "despite the lack of initial response, that the nonresponders still demonstrate benefit over their baseline status at 1-year follow-up." They also noted: "It is probable that there is a significantly positive benefit to the 30 or more hours of contact patients experienced. It has been well demonstrated that recurrent patient visits may improve health and quality of life measures as an independent variable."

Medicare Population
One article compared IEPR data for those above 80 years of age to those below that age (Linnemeier, Michaels et al. 2003). This study analyzed 3,037 patients including 249 octagenerians from 80 centers in the US and abroad. Entry criteria are listed as informed consent and at least 1 hour of ECP treatment for angina, but an analysis of those excluded is not given. Fewer patients in the octagenerian group completed therapy as compared to younger patients (76% vs. 84%; p < 0.01) with the authors noting "failure to complete a course of treatment in the elderly population was frequently due to an intervening non-cardiac medical event or patient choice." These patients who failed to complete treatment were excluded from the analysis. It is not clear how these patients differed from those who were analyzed. Of those who completed treatment, the authors report a 76% reduction in angina class "by greater than or equal to one class"(follow-up time for this measure is listed as "post treatment" but it is not clear when following treatment this measure was taken) (Linnemeier, Michaels et al. 2003). Weekly angina episodes and nitroglycerin use were decreased by six episodes in the elderly but the statistical significance of this difference is not given and again it is not clear when after treatment this measure was taken. Only 57% of the elderly were on beta blockers, 69% were on aspirin, and 46% were on lipid-lowering therapy, although the authors state that patients referred for ECP were considered optimally medically managed. They also state that no attempt was made to maintain current medication regimens during the study, so it was possible that medications and other therapies were changed during the course of ECP therapy. It was reported that assessed quality of life, health and satisfaction were improved post-treatment (p < 0.001 for each), but it is unknown if validated measures were used as the data were reported only by a bar graph with the percent of patients who reported good, very good, or excellent on each measure before and after ECP. Six-month follow up of 183 patients was done during a telephone interview, with 81% reporting maintenance of angina improvement.

Morbidity

A retrospective study of 58 patients with CCSC class II, III or IV who met inclusion/exclusion criteria were treated with standard ECP (35 one-hour sessions with cuff pressures of 250-310 mm Hg) (Weisfogel, Schaffer et al. 2001). The authors listed five outcomes. For CCSC, the pretreatment functional class was 2.67 ± 0.71 and the post-treatment functional class was 1.71 ± 0.65, with a p value listed as 7.32×10^{-12}. The study did not make clear the difference between a functional class of 2.67 versus 1.71, other than statistical significance. Percent improvement in angina symptoms was given, with no pre and post comparison, as 42% having 50+ % improvement, 11% having 25% - 49% improvement, and 5% having 0% to 24% improvement. The average number of angina episodes over 24 hours pretreatment was 1.59 ± 2.86 and post-treatment was 0.31 ± 0.57. Sublingual nitroglycerin consumption per day pretreatment was 0.62 ± 0.71 and post-treatment 0.14 ± 0.33. Only 24 patients were included in the analysis of hospitalizations for angina per patient over 6 months of follow-up. Hospitalizations pretreatment were 1.17 ± 0.38 and post-treatment 0.04 ± 0.20 (apparently some who were not hospitalized pretreatment were hospitalized post-treatment) with the p value listed as 1.02×10^{-16}. Hospitalizations for other causes such as congestive heart failure were not listed or compared.

Perfusion studies
In a study published in 2003, 25 patients treated with ECP underwent an exercise test with a Bruce protocol comparing SPECT scans pre- and post- ECP treatment (Tartaglia, Stenerson et al. 2003). There were no controls. ECP (done in "standardized fashion") post-treatment measures showed an improvement in heart rate-blood pressure product of 18,891 ± 3,939 to 20,464 ± 4,305 ($p < 0.03$), and a reduction in radionuclide perfusion score by ischemic segments (16.36 ± 10.52 to 14.12 ± 10.9, $p < 0.05$). Most patients (21 of 25) had a reduction in at least one angina class. More than half of the patients (16 of 25) had improved nuclear scores on the stress study exercise time (449.3 seconds compared to 357.2 seconds pre-ECP, with one apparently significant outlier). The clinical significance of these changes was not discussed. There were 16 of 25 patients with ST-segment depression on the pre-ECP exercise treadmill test. Post ECP, 3 of those 16 patients had no ST-segment depression on their ETT and 10 of the 16 patients had a statistically significant delay in their time to ST-segment depression (though there appeared to be one extreme outlier). Inclusion criteria included the capability of exercising on a treadmill according to a Bruce protocol, and it was mentioned that it was not possible to eliminate an exercise training effect.

In 2001, investigators in Japan reported on 12 patients with documented ischemia (8 patients had functional angina and 4 patients had silent myocardial ischemia) who while hospitalized underwent 35 sessions of ECP and had exercise thallium-201 scintigraphy, gated blood pool cardiac scintigraphy and cardiac catheterization before and after treatment (Urano, Ikeda et al. 2001). Exclusion criteria were the same listed as for MUST-EECP. The investigators described a control period of 38 ± 9 days during which the patients were in the hospital and engaged in sedentary or mild activity. Baseline testing was performed during this time. The next phase of treatment was 35 hours of ECP given once or twice per day, for a total of 36 ± 6 days. In this study, the cuff pressure was set at 300mm Hg, with a mean diastolic to systolic pressure ratio of 1.1 ± 0.4. Exercise thallium was performed at the same cardiac workload before and after treatment. Values were presented as means standard deviation or percentages. Comparisons used paired Student t-test, and multiple comparisons were analyzed by repeated measures analysis of variance. Exercise parameters (exercise duration, exercise tolerance, time to 1-mm ST segment depression, rate pressure product at peak exercise and a 1-mm ST segment depression) were not significantly different at baseline or before treatment but improved after treatment ($p < 0.05$). Myocardial perfusion abnormalities decreased after treatment (50% to 33%, $p < 0.01$). The plasma levels of brain naturetic protein decreased after treatment ($p < 0.05$). Left ventricular systolic and diastolic function was assessed by cardiac cath and noninvasive radionuclide angiography. Ejection fraction systolic indexes were not changed. Left ventricular end diastolic pressure decreased and diastolic indexes improved after treatment. It is of note that no patient during this study experienced angina, which seems to be attributed to the fact that they were in the hospital. No explanation was provided how hospitalization eliminated angina episodes.

In a study published in 2002, the International Study Group enrolled 175 patients (case series) (88% men, mean age 61 ± 9.5 years), apparently over a period of 7 years (Stys, Lawson et al. 2002). Patients had a baseline pre-ECP radionuclide perfusion treadmill stress test (RPST) within a month before ECP and then within 6 months of completing ECP treatment. The maximal external compression used in this study was 225 to 275 mm Hg. Anginal medication adjustment was determined by patients and their physicians, and the changes were documented (it was not stated what they were controlled for in the final analysis). Eigthy-five percent reported improvement in angina of $\geq$ 1 CCS angina class, 15% reported improvement by $\geq$ 2 classes. Post exercise tests were to two different endpoints – one to the same level of exercise pre and post ECP, and the other to maximal cardiac workload post ECP. In centers that exercised to the same level pre and post ECP, 83% had improvement in RPST perfusion defects; 16% had no improvement. No correlation for angina symptoms was given (also, data and statistical significance were not given for the RPST). In this group of patients, the post exercise time was not statistically significant from the pre-exercise time, and the double product (blood pressure x heart rate) decreased ($p < 0.05$). The lower double product was reported as "analogous to the peripheral vascular conditioning effect seen with exercise, in which improved vasomotor tone decreases the blood pressure response to exercise." In patients who underwent post ECP maximal RPST, exercise duration improved (6.61 ± 1.88 minutes pre-ECP versus 7.41 ± 2.03 minutes post-ECP, $p < 0.0001$), with no change in double product. In this group, 54% showed improvement in RPST defect, 42% had unchanged defects, and 3% had a worsening.

A study in 2004 looked at the effect of enhanced external counterpulsation (at least 35 one-hour sessions at 300 mm Hg cuff pressure) in 23 consecutive patients with angina who had a positive dobutamine stress echocardiogram (Bagger, Hall et al. 2004). "Established exclusion criteria" were used. In this study, 10 patients had an improvement of $\geq$ 2 grades in the stress-induced wall motion score, whereas the remaining 13 did not show improvement. Interestingly, those who showed improvement on the dobutamine stress echocardiogram had a greater increase in diastolic augmentation ratio (1.2 ± 0.6 versus 0.5 ± 0.5, $p = 0.01$), but the CCS angina class results after enhanced external counterpulsation and exercise comparison between the two groups had non-significant p values.

In 2001, a study examined the psychosocial effects of ECP treatment on 27 patients, and included pre and post ECP thallium scans (Springer, Fife et al. 2001). Of the 27 patients, 17 were categorized as "improved" on myocardial perfusion on stress thallium post ECP in that reversible defects were resolved, and 10 of 27 had unchanged perfusion scans. Both the improved and unchanged groups rated overall well-being as improved, as was chest pain frequency per week, chest pain severity, and nitrate use frequency per week. Results were statistically significant whether or not there was an improvement in the thallium scan. In examining the psychosocial effects of ECP, there was improvement in levels of depression, anxiety and somatization, but no change in levels of anger or hostility for either group of patients. The authors concluded that "on most measures, change was more significant for subjects who showed objective evidence of resolution of ischemia."

Hemodynamic effects
A 2001 study examined 1,004 IEPR patients for diastolic augmentation (DA) as it had been proposed that maximum hemodynamic effects occur when the ratio of diastolic to systolic pressure is in the range of 1.5 to 2.0 (Michaels, Kennard et al. 2001). At the completion of ECP treatment, patients were analyzed by groups with a DA ratio of either < 1.5 or $\geq$ 1.5. Only 37% of the 1,004 study patients achieved a DA $\geq$ 1.5. Patients in the low DA group appeared to have worse clinical outcomes (unstable angina, CHF, and higher angina class, $p < 0.05$ or better), but baseline variables between the two groups were not reported. Factors associated with lower DA ratio included age $\geq$ 65, female gender, left ventricular ejection fraction < 35%, hypertension, prior coronary bypass surgery, noncardiac vascular disease, multivessel disease, congestive heart failure, current smoking, unsuitability for further revascularization, and higher baseline angina class. The authors stated "the incidence of congestive heart failure exacerbation and the improvement in angina class appear to be related to the degree of DA with EECP." This article concluded that "DA is important in achieving maximal clinical benefit from EECP."

A 2002 examination of IEPR data of 2,486 patients for the relationship of diastolic augmentation to clinical benefit was similar to the previous article (Lakshmi, Kennard et al. 2002). In this study, 1,009 patients had a DA ratio below or equal to the median level both at the beginning (0.7) and end (1.0) of EECP. Some of the factors associated with a DA ratio below the median were very similar to the previous study (female gender, noncardiac vascular disease, age 65, smoking, heart failure, diabetes, hypertension, prior coronary artery bypass surgery – it was unclear what other variables were examined). The authors suggested that the patients who had the greatest increase in the DA ratio from beginning to end of treatment had the greatest reduction in angina class. Regardless of the DA ratio change (even in the 250 who after treatment went in the opposite direction – from 1.0 to 0.7), there appeared to be a response as judged by a reduction in angina class.

Stys, et al., examined the hemodynamic effect of EECP in IEPR data (Stys, Lawson et al. 2001). The authors reported that the hemodynamic effect of EECP did not predict improvement in CCS angina class (the initial and final effectiveness ratios were similar in patients with and without improvement in CCS angina class).

A 1985 study by Kern, et al., measured coronary and systemic hemodynamics before, during, and after ECP treatment in 14 patients with coronary artery disease and normal left ventricular function (Kern, Henry et al. 1985). A triple thermistor coronary sinus thermodilution catheter introduced via an antecubital vein and a balloon -tipped pulmonary artery catheter measured right atrial, phasic, and mean pulmonary artery pressure and cardiac output, and a dual micromanomter transducer tipped catheter measured left ventricular and aortic pressures. While they found an increase in the arterial pressure (108 ± 11 to 114 ± 12 mm Hg, $p < 0.01$) and diastolic pressure-time index (440 ± 51 to 498 ± 82 units, $p < 0.01$), they found no change in the systolic pressure-time index, or absolute coronary sinus, or great cardiac vein blood flow. The authors concluded that external diastolic pressure augmentation did not affect heart rate, right heart hemodynamics, cardiac output or calculated myocardial oxygen consumption.

Canadian Cardiovascular Society Classification II (CCSC II)
The evidence presented for inclusion of CCSC II in Medicare coverage comes from two sources: 1) a 1999 subgroup analysis of the MUST-EECP study (not separately published); and 2) IEPR subgroup analysis originally from 2 year follow-up data published in 2004, with Class II data not separately published in the article (Michaels, Linnemeier et al. 2004). CMS applies less weight to evidence that is not first published in a peer-reviewed journal. The original published 2004 study includes 1,097 registry patients from the IEPR of which 95% were white and 74% were male. Outcomes were measured by telephone follow-up. Outcomes are angina class and quality of life assessment using 5-point scales for health status, quality of life, and satisfaction with quality of life (unknown if measures are validated). Of the patients starting ECP, 82% completed 35 hours of therapy, with 10% and 8% discontinuing therapy because of clinical events and patient's preference. Of the total cohort immediately after completion of ECP treatment, 73% of patients had a decrease in angina class of ≥ 1, 26% had no change in angina class, and 1% had an increase in angina class. Fifty percent reported improved quality-of-life. At two year follow-up, 74.9% reported angina class reduction, although it is not clear how drop-outs from the start of the study or failure to follow-up was addressed. Quality-of-life assessment is reported as being sustained at the 2-year follow-up. In the 2004 article, the authors acknowledged, "A primary limitation of this analysis was the lack of a control group to assess the extent of the reported improvement due to other interventions (i.e., medical therapy, lifestyle modifications, coronary revascularization) or to a "placebo effect" that may be expected in a population of highly symptomatic patients enthusiastic for an emerging novel treatment." They also stated, "This observational registry study cannot directly evaluate whether the anti-ischemic effects observed in the randomized Multicenter Study of Enhanced External Counterpulsation trial extends to a broader population of patients treated with EECP. Self-reported severity of angina based on mail or telephone interview is subject to potential bias, although coordinators in the IPR were trained in assessing and defining follow-up symptoms."

In 2000, in a case series study of 2,289 patients from the IEPR data, CCS functional class I and II patients "were grouped together to provide a reference for this analysis because they were unable to show further improvement in functional class with treatment" (Lawson, Hui et al. 2000). Patients in this study had varying treatment times (average treatment time was 33.43 ± 12.3 hr), with the author's conclusion being "the dose effects of EECP remain speculative." Characteristics of patients were 92.4% white and 79.7% male. Average age was 65.8 ± 10.7 years (range 19 years – 97 years). The average CCS anginal class before treatment of 2.78 improved to an average of 1.81 after treatment ($p < 0.001$). The authors stated that patients in CCS III and IV were significantly more likely to demonstrate functional improvement. Odds for improvement for pre-ECP CCSC IV were given as 3.30 (2.49 – 4.39) and for pre-ECP III as 4.38 (3.46 – 5.56). The odds for class I or II were not given.

Indication 2 - Heart Failure

Evidence supporting expansion of ECP to congestive heart failure includes data from the IEPR (which is used to track acute and long-term outcomes for consecutive patients treated for chronic angina), a 26 patient feasibility study in euvolemic patients, and Cardiomedics registry data. Results of the prospective evaluation of EECP in heart failure (PEECH) trial have not yet been published in a peer-reviewed journal thus less weight is being given to this evidence. IEPR data was used in a study published in 2001 comparing ECP outcomes for refractory angina in 548 patients with a history of congestive heart failure (CHF) to 1,409 patients without a history of CHF, looking at adverse events and CCS angina class (qualifying CHF criteria not specified) (Lawson, Kennard et al. 2001). The mean age of the study group was 67.1 ± 10.9 years, and 72% were male (racial/ethnic demographics not presented). Though "EECP was typically prescribed for 35 1-hour sessions over a period of 7 weeks", mean treatment hours varied, reported as 34.7 ± 10.2 hours for those without a history of CHF and 33.1 ± 10.8 hours for those with a history of CHF ($p < 0.001$). In this observational study, the history of CHF group had fewer patients complete the course of EECP (78% completed the course as prescribed versus 86% of those without a history of CHF, $p < 0.001$). Angina class improved one or more classes in 68% of the history of CHF group and in 75% in those without a history of CHF ($p < 0.01$). It worsened in 0.9% of those with history of CHF. At 6 months, patients with a history of CHF reported maintenance of reduced angina, but were more likely to report a major adverse event (death: 7.9% versus 2.2%, $p < 0.001$; cardiac hospitalization: 19.1% versus 13.6%, $p < 0.01$; major adverse cardiac event: 14.4% versus 8.6%, $p < 0.001$).

In a 2002 study of IEPR data left ventricular dysfunction was defined as ejection fraction (EF) $\leq$ 35% (recorded prior to ECP therapy, but time range of measurements not given) (Soran, Kennard et al. 2002). The study included 1,402 patients with 77.7% LVEF > 35% and 22.3% LVEF $\leq$ 35%. Patient characteristics show the group with left ventricular dysfunction to have more patients in CCSC III/IV (86.2% v. 73.6%, p value not given), greater multivessel disease (89.8% v. 76.5%, $p < 0.001$), and more unstable angina (4.8% v. 1.7%, p value NS). Patients with an ejection fraction $\leq$ 35% were less likely to complete a course of treatment (79.4% vs. 85.8%, $p < 0.01$) with the reason for stopping treatment more likely to be a clinical event (14.4% vs. 7.2% with $p < 0.001$). Six-month data were available on 84% of the initial 1,402 patients. Patients with the lower EF had greater 6-month mortality (9.3%) versus those with the higher EF (2.2%, $p < 0.001$). Six month post-treatment results (for those patients reporting anginal status) include 81.0% of the $\leq$ 35% LVEF group and 83.8% of the LVEF > 35% having either no change in angina or less angina than immediately post-ECP treatment ($p = NS$).

A 2005 IEPR study reported data for 746 patients with angina and with a history of heart failure (Lawson, Silver et al. 2005). Patients were divided into two groups: LVEF $\leq$ 35% (diastolic dysfunction as defined by the article) and LVEF > 35% (systolic dysfunction as defined by the article). Standard ECP treatment was prescribed (35 hours, pressures not noted) with 79.3% of the diastolic dysfunction (DD) group and 76.9% of the systolic dysfunction (SD) group completing the course of treatment (p = NS). CCS anginal class was reduced by $\geq$ 1 class in 71.9% of DD patients versus 72.2% of the SD patients (no p value given), with similar decreases in anginal episodes and nitroglycerin use. No measurement of ejection fraction was made post treatment. At one year, decreased angina was reported as 78.1% of DD patients and 75.8% of SD patients as compared to pretreatment (p = NS) (not all subjects were available for the telephone follow-up). Fifteen months after the first hour of EECP, death occurred in 14.1% for the DD group and in 9.2 % of the SD group (p = 0.039). Major adverse events (death, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention) occurred in 23.8% for the DD group and 24.4% of the SD group (p = 0.98).

A 2002 feasibility study for ECP treatment of NYHA class II/III was undertaken in 26 patients (Soran, Fleishman et al. 2002). Exclusion criteria for this study included exercise limited by chest pain, EKG changes consistent with myocardial ischemia, unstable angina, and others. Inclusion criteria were that patients had to have the ability to exercise on a treadmill (Modified Naughton Protocol) with exertion limited by either shortness of breath or fatigue, and heart failure treatment must have been optimized and stable (demonstrated as an absence of medication changes over the 2 weeks prior to the first study visit) prior to enrollment. Age was 56.3 ± 16.1 years, with 18.8% females. Peak oxygen uptake, quality of life, and exercise duration were outcome measures. Statistical analysis was performed by comparing mean changes of the outcome measures from baseline to one-week post treatment and to the end of the study (presumed 6 month follow-up), using paired t tests. Peak oxygen uptake in 23 patients increased from the mean baseline value of 14.99 to a mean of 15.98 mL/kg/min (se ± 3.57% min - 27.09% max + 43.57%; p = 0.05) at one week follow-up. Nineteen patients completed the 6 month follow-up, with peak oxygen uptake increased from mean baseline of 14.78 to a mean of 18.41 mL/kg/min (se ± 34.71% min - 0.46 % max + 62.76%; p < 0.001). Exercise duration (unclear if this was measured in 23 subjects) increased from the baseline value of 637.63 seconds to 732.96 seconds (se ± 4.89% min - 7.66% max + 89.58%; p < 0.001) at one week follow-up. At 6 month follow-up (19 patients), exercise duration increased from 637.13 seconds to 715.17 seconds (se ± 6.53% min - 15.20 % max + 81.02%; p < 0.028). Quality of life data using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) was assessed at baseline, one week post treatment follow-up (24 patients), and 6 month follow-up (22 patients). The authors reported that "the overall changes between the test results at baseline and one-week post-treatment were significant (p < 0.01) for total score, physical dimension and emotional dimension. In the 22 patients who completed the study and had the MLHFQ at 6-month follow-up visit, total score showed persistent improvement over baseline values, but only the change in emotional dimension remained significant (p < 0.01)."

A 2005 report of 127 Cardiomedics ECP registry patients examined the effect of treatment in patients with NYHA class II-IV CHF patients (Vijayaraghaven, Santora et al. 2005). CHF inclusion criteria were symptoms and signs of CHF with shortness of breath, leg edema, or significant fatigue. Patients were treated with lower pressures. The authors stated "the high pressures and resulting 1.5:1-2:1 peak diastolic to peak systolic pressure (D/S) ratios shown to be optimal in the treatment of angina can cause excessive preload and adverse effects in congestive heart failure (CHF) patients, particularly those with left ventricular ejection fractions < 40%". In this study, pressures and resultant D/S ratios (referred to as DA ratios in other articles) started as low as 0.1:1. Patients were divided into three groups based on the post-hoc resultant average diastolic augmentation ratio. The resultant average D/S ratios in the three groups were 0.7:1 in the low group, 1.08:1 in the middle group and 1.32:1 in the high group. The outcomes examined were comparative changes in mortality, LVEF, NYHA CHF class, and incidence of all-cause hospitalizations for a period of 1 year following the therapy. For statistical purposes, measurements were mean D/S ratio, with individual variable differences determined using the Student t test and the chi-square test. As with other ECP studies, there was a preponderance of men (> 79%); race/ethnicity were not listed. Although in all three groups medical therapy is in accordance with accepted medical practice, only 55% of patients in one group were reported to receive angiotension-converting enzyme inhibitors (versus 74.4 and 81.5 in the other groups), and only 23.3 – 31.4% of enrollees received beta blockers, despite diagnoses of angina with documented evidence of coronary artery disease and CHF. Therapy breakdown one year post ECP therapy was not given. It was not stated if treatment changes (i.e. medications, lifestyle) during or after ECP were adjusted for.

Table 2. Left Ventricular Ejection Fractions of Surviving Patients

Group	Before ECP (%)	Year After ECP (%)	p value
Low D/S ratio(n=53)	32.6 ± 7.2	40.1 ± 26.9	< 0.05
Mid D/S ratio(n=36)	31.3 ± 11.6	37.5 ± 27.5	NS
High D/S ratio(n=31)	32.6 ± 20.4	38.3 ± 14.7	NS

Table 3. New York Heart Association Congestive Heart Failure Classification of Surviving Patients

Group	Before ECP	Year After ECP	p value
Low D/S ratio(n=53)	3.7 ± 1.0	1.9 ± 0.5	< 0.0001
Mid D/S ratio(n=36)	2.7 ± 1.3	1.9 ± 0.5	< 0.005
High D/S ratio(n=31)	2.7 ± 1.3	1.9 ± 0.5	< 0.01

Table 4. Annual Average Number of All-Cause Hospital Admissions per Patient

Group	Before ECP	Year After ECP	p value

Table 4. Annual Average Number of All-Cause Hospital Admissions per Patient			
Low D/S ratio(n=54)	2.8 ± 1.6	0.35 ± 0.5	< 0.0001
Mid D/S ratio(n=39)	2.5 ± 1.4	0.42 ± 0.5	< 0.0001
High D/S ratio(n=34)	1.3 ± 1.7	0.70 ± 0.5	< 0.01

The number of patients analyzed for hospital admissions was not the same as the number of patients analyzed for LVEF or NYHA class. It was not clear if the average annual number of all-cause hospital admissions per patient was adjusted for comorbidities. The incidence of all-cause hospital admission per patient was given by D/S ratio, not CHF class.

Table 5. Mortality: Comparisons Between Groups				
Study Group (NYHA Class)	Mortality (%)	Comparison Group (NYHA Class)	Mortality (%)	p value
Low D/S ratio(II-III)	0.00	MADIT II (II-III)	8.50	< 0.0001
Low D/S ratio(III-IV)	2.10	COMPANION (III-IV)	12.20	< 0.0001
Low D/S ratio(II-IV)	1.85	Mid D/S (II-IV)	7.69	< 0.0001

Table 5. Mortality: Comparisons Between Groups				
Low D/S ratio(II-IV)	1.85	High D/S (II-IV)	8.82	< 0.0001
Mid D/S ratio(II-IV)	7.50	High D/S (II-IV)	8.33	NS

A mortality reduction was suggested when the three D/S ratio groups were compared, i.e. low ratio compared to mid and high ratio where risk comparison is based on the post-hoc group assignment. The authors used the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) and the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) studies for additional mortality comparisons.

CMS has been informed by Vasomedical that results of the Prospective Evaluation of EECP in Congestive Heart Failure (PEECH), which was presented at the American College of Cardiology 2005 Annual Scientific Session, have been accepted for publication. Subjects (187) with mild to moderate symptoms of heart failure were randomized to either ECP treatment (applied pressure of 300 mm Hg) and protocol-defined pharmacologic therapy (PT) or PT alone. Two co-primary end points were predefined: the percentage of subjects with a 60 second or more increase in exercise duration and the percentage of subjects with at least 1.25 ml/min/kg increase in peak VO_2(peak oxygen uptake) at six months. After six months, 35% of EECP patients and 25% of control patients increased their exercise duration by at least 60 seconds (p = 0.016). NYHA functional class improved in 31% of EECP patients compared with 16% in the control group and EECP patients reported a greater improvement in quality of life. However, there was no significant difference in peak VO_2 between the two study groups (Kerr 2005).

Indication 3 - Cardiogenic Shock

Three studies were reviewed for this indication.

A 2000 study of 39 patients in Japan compared the intra-aortic balloon pump (IABP) to ECP in patients with acute myocardial infarction, after balloon coronary angioplasty (Taguchi, Kenichi et al. 2000). Twelve patients (Killip class on admission I or II) had an IABP placed in the cardiac catheterization laboratory due to intracoronary thrombosis observed during coronary angioplasty. ECP was performed on another 27 patients (Killip class 1) 2 or 3 days after admission. Hemodynamics were measured invasively in both groups. The ECP measurements were taken at baseline and then during treatment at 15 minutes, 30 minutes, 45 minutes, 60 minutes, and 60 minutes after treatment. In the IABP group, baseline measurements were obtained > 60 minutes after setting of minimal IABP effect to achieve a static hemodynamic condition and to avoid blood clots on the IABP balloon surface. The 15, 30, 45, and 60 minute measurements were obtained after starting full support of IABP and the last measurement obtained 60 minutes after returning to a minimal IABP effect. The authors reported: "Mean values of heart rate did not change significantly in either group before, during, and after treatments. Mean values of heart rate at baseline and during and after treatments did not show significant differences between the 2 groups. Mean values of right atrial pressure increased significantly at 15 and 30 minutes after starting EECP compared with values at baseline, then decreased gradually. There was no significant increase in right atrial pressure 45 and 60 minutes after starting EECP compared with baseline value. Although mean values of right atrial pressure did not change in the IABP group, there was no significant difference at any measuring time point between 2 groups, except at 15 minutes after starting treatment. Mean values of pulmonary capillary wedge pressure in the EECP group increased significantly at 15 and 30 minutes after starting EECP, and then decreased gradually, but no significant change was seen in the IABP group. Differences of mean values between the 2 groups were not significant at baseline and during treatment. However, the mean value at 60 minutes after stopping treatment was significantly lower in the EECP group than in the IABP group. Mean values of cardiac index increased significantly at 45 and 60 minutes after starting treatment compared with the baseline value in the EECP group. However, no significant change was observed in the IABP group. The mean value of cardiac index at 60 minutes after starting treatment in the EECP group was significantly greater than that in the IABP group. Mean values of the areas under the artery pressure curves during the diastolic phase increased significantly compared with baseline value at every measurement point during treatment in the EECP group, and at 45 and 60 minutes in the IABP group. There was no significant difference between the 2 groups at any measuring point. Mean values of the areas under the artery pressure curves during the systolic phase decreased significantly during treatment compared with baseline in the IABP group. No significant change was observed, however, in the EECP group. Mean values in the IABP group were significantly lower than those in the EECP group at every measuring point during treatment. Mean values of systolic systemic vascular resistance decreased significantly during treatment compared with baseline values in both groups. No significant difference in systolic systemic vascular resistance between the 2 groups was observed at any measuring point." While outcomes were measured as hemodynamic comparisons at specified times, it was noted that measurement time from admission was not the same in the groups. Additionally, intra-aortic balloon pumps are generally administered in unstable hemodynamic states, whereas the hemodynamic state of these subjects was stable.

A 2002 case series included 10 hemodynamically stable patients who underwent left heart catheterization and coronary angiography from the right radial artery for diagnostic evaluation (Michaels, Accad et al. 2002). At baseline and then during ECP (external cuff pressures ranging from 100 to 300 mm Hg), hemodynamics were measured in unobstructed coronary arteries and included central aortic pressure (using a coronary catheter), intracoronary pressure (a sensor-tipped high-fidelity pressure guidewire), and Doppler flow velocity (a Doppler flow guidewire). ECP resulted in an increase in diastolic (71 ± 10 mm Hg at baseline to 137 ± 21 mm Hg during EECP, $p < 0.0001$) and mean intracoronary pressures (88 ± 9 to 102 ± 16 mm Hg, $p = 0.006$) and a decrease in systolic pressure (116 ± 20 to 99 ± 26 mm Hg, $p = 0.002$).

A 1974 case series study of 20 patients who were clinically diagnosed with cardiogenic shock after myocardial infarction were treated with ECP (Soroff, Cloutier et al. 1974). Other treatments included a transvenous pacemaker and digitalis if needed, assisted ventilation through an endotracheal tube or oxygen by mask or nasal canula, intravenous fluids and/or sodium bicarbonate if needed, metarmial bitartrate, isoproterenol, mephentemine, methylprednisoline, chlorpromazine, dexamethasone, levartarenol, and hydrocortisone. Eleven patients died during or soon after treatment. Two more patients died within 3 weeks but were counted as survivors in the analysis. Seven patients were discharged from the hospital. The study claims that the 45% survival rate with ECP (which included the two short term survivors) was an improvement ($p < 0.01$) over the usual 15% survival rate of cardiogenic shock.

Indication 4 - Acute Myocardial Infarction

A 1980 study randomized (based on allocation by a coordinating center) 258 acute myocardial infarction patients to either 4 or more hours of ECP within 24 hours of admission or to control (Amsterdam, Banas et al. 1980). Diagnosis of MI was on the basis of "classic history, characteristic ECG evolutionary changes and typical serum enzyme changes." Left ventricular function was judged on clinical exam and x-ray changes. Other treatment included antiarrhythmic drugs, diuretic agents, digitalis, vasodilator drugs and propranolol, and analgesic or sedative therapy. In the group receiving 4 or more hours of ECP within the first 24 hours after admission, the mortality rate was 6.5% in the treatment group versus 14.7% in the control group (p < 0.05). Also, for the group of patients with 3 or more hours of treatment, ECP was associated with a lower morbidity as defined by recurrent chest pain, progression of cardiac failure, occurrence of ventricular fibrillation, change in heart size and clinical cardiac functional status at discharge, with p values ranging from < 0.05 to < 0.01.

4. MCAC

The MCAC was not held for this topic.

5. Evidence-based Guidelines

The American College of Cardiology/American Heart Association (ACC/AHA) 2002 "Guideline Update for the Management of Patients with Chronic Stable Angina-Summary Article" is a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. The level of evidence assigned to ECP is Class IIb, "usefulness/efficacy is less well established by evidence/opinion", which is their lowest level of evidence suggesting there may be some benefit. It is further stated "additional clinical trial data are necessary before this technology can be recommended definitely" (Gibbons, Abrams et al. 2003).

In "Primary care management of chronic stable angina and asymptomatic suspected or known coronary artery disease: a clinical practice guideline from the American College of Physicians", under alternative therapies for patients with refractory angina, "evidence is still lacking for the use of …, enhanced external counterpulsation…" Additionally stated, "these techniques should be used only in patients who cannot be managed adequately by medical therapy and who are not candidates for revascularization (interventional or surgical)" (Snow, Barry et al. 2004). Disabling Class III and IV angina in these specific circumstances is currently covered by Medicare.

The ACC/AHA 2005 Guidelines for the Evaluation and Management of Chronic Heart Failure in the Adult states: "External Counterpulsation. The technique of external counterpulsation involves the use of a device with inflatable cuffs that surround the lower limbs and inflate and deflate in synchronization with the cardiac cycle. The device is designed to reduce loading conditions in systole while increasing coronary perfusion pressures in diastole. External counterpulsation has been shown to reduce the frequency and severity of anginal attacks in patients with symptomatic coronary artery disease. A possible mechanism of action for its observed clinical effect may be an improvement in endothelial function of the coronary vascular bed. Early trials of this therapy in patients with HF and low EF have been encouraging, and a randomized trial has been completed recently. Until more data are available, routine use of this therapy cannot be recommended for the management of patients with symptomatic reduced LVEF" (Hunt, Abraham et al 2005).

The ACC/AHA does not mention external counterpulsation in the guidelines for acute myocardial infarction management (Ryan, Anderson et al. 1996).

In the emergency management of patients with cardiogenic shock algorithm, ECP is not listed (Harrison's online 2005).

6. Public Comments

During the initial comment period, CMS received comments from one professional society (The American Society of Cardiology [ACC]), three primary authors of ECP articles, and eighty general public comments. The ACC did not believe the current evidence was adequate to evaluate health outcomes of ECP for the conditions identified. The three primary authors supported the expansion of coverage to some of the conditions identified. Of the eighty general public comments, seventy nine supported the use of ECP therapy. Those comments can be found on our website and the complete summary can be found in our proposed decision memorandum.

Comments on the Proposed Decision Memorandum

CMS received a total of 462 comments on the proposed decision memorandum. Of the 462 comments, 142 comments were posted to our website during the public comment period. CMS received the remaining 320 comments through the mail or by e-mail, and scanned and subsequently posted them to the CMS website.

Of the 320 comments not submitted to the web site, 235 were exact copies of a form letter supplied by Vasomedical, Inc. (one of two requestors of this national coverage analysis) to ECP providers and signed by patients (or, on a few occasions, by patient's families) sharing the patient's experience after ECP therapy. The form letter stated, "EECP therapy truly changed the quality of my life and everyone who is a candidate for this non-invasive, inexpensive treatment should have the same opportunity I was given." The form letter did not refer to the content of the decision memorandum.

Of the remaining hard copy letters, 45 comments were variations of the form letter with individual comments written on them by the patients or original letters from patients providing testimonials regarding their experiences with ECP therapy. Fourteen testimonials were provided by one physician practice. Seventeen hard copy or e-mail comments from physicians were received (two addressed to the American College of Cardiology and copied to CMS), of which 5 contained some exact phasing from a Vasomedical letter sent out in December of 2005 to providers of EECP. In addition, 5 non-physician providers of ECP therapy sent hard copy comments as well as one friend of a patient. We also received comments from the requestor, Vasomedical, and from Cardiomedics who had submitted a request for an NCD subsequent to our opening this NCD.

Of the 142 comments submitted to CMS the web site, one was from a professional society, 84 were from providers (includes non-physician and physician providers) of ECP therapy, 23 were identified as being from patients, one was from a sales director for Vasomedical and one was from a consultant to Vasomedical. The remaining were from the general public.

Some commentors referenced evidence without specific reference to an article; however 41 commentors did specifically refer to evidence.

A. Professional Societies

The American College of Cardiology (ACC) commented favorably on the proposed decision, saying, "The ACC supports this decision and believes that it is consistent with currently available evidence."

B. Expert Opinion

Six comments were directed to CMS by primary authors of ECP articles. Three of the six comments referred to specific evidence other than the PEECH trial. These references are addressed in the Comments with Evidence section below.

C. Comments with Evidence

Forty-one of the comments referenced specific studies or trials. Of the 41, thirty-one of these referred only to the PEECH trial. CMS was provided a confidential copy of the PEECH trial manuscript during this national coverage analysis. However, since the manuscript is not yet published, the public does not have access to the complete information about the PEECH trial results. Since the manuscript provided to CMS was confidential, we are unable to provide any significant response, other than what was previously stated in the proposed decision memorandum.

CMS has reviewed and considered the other submitted evidence, which is listed completely in Appendix C. The submitted evidence is reviewed below by study design for organizational purposes. The references that were not previously included in the proposed decision memorandum are addressed below.

Randomized clinical trials of ECP:

- No additional randomized clinical trials were brought to the attention of CMS.

Other comparative studies of ECP:

- Shechter 2003 (4) is a nonrandomized, unblinded study of 40 patients with Class III/IV angina, with the comparison group being patients who refused ECP therapy. The subjective outcomes, nitroglycerin use and CCS class, could be subject to the placebo effect, as the control group was self-selected as probably having less enthusiasm for this procedure (Blue Cross Blue Shield 2006). Importantly, class III/IV angina is already covered and no additional information for the suggested expansion group is provided.

ECP case series studies, single center:

- Bonetti 2003 (3), Masuda 2004(7), Masuda 1999 (8), Lawson 1996(11), Aurora 2005 (19), Taguchi 2004(12), and Masuda 2001(14) have various physiologic outcome measures ranging from endothelial function to nitric oxide levels that could suggest many mechanisms for the effects of ECP, though there are no controls in these short term (a month after last therapy or less) studies. These small ($\leq$ 50 patients) studies are based on physiologic outcomes in an attempt to understand the mechanism of action of ECP. They do not provide information about the clinical effectiveness of the treatment.

- Lawson 1992 (21) and Lawson 1995 (22) are small ($\leq$ 18 patients) case series studies (apparently the same group) of chronic angina patients (CCS class not listed) that are suggested as evidence for expansion to CCSC II angina. CMS notes that no distinction in patient CCS class is given, so CCSC II is not mentioned explicitly in either article.
- Strobeck 1998 (30) discusses the treatment of 3 patients, and adds little to the evidence base.
- Wright 1975(32), Cohen 1973 (33), and Watson 1976 (34) refer to ECP treatment of cardiogenic shock studies in the 1970's. None of these articles provides current relevant information as to the evidence of health benefit for ECP treatment in cardiogenic shock in the Medicare population.
- Applebaum 1997 (35) reports on carotid artery blood flow and renal artery blood flow in patients with atherosclerosis, and is not relevant to the indications requested in this NCD.
- Tartaglia 2003 (10), Michaels 2002 (5), Urano 2001(6), Lawson 2000 (23), Suresh 1998 (25), Soroff 1974 (31) have been cited in this decision memorandum, and the commenters provided no information that disagreed with our interpretation of these articles.

ECP case series, multicenter:

- Michaels 2005 (2) was provided as evidence that ECP therapy reduces angina and improves exercise capacity, though in this study the authors "sought to critically evaluate and quantify the effect of EECP on myocardial perfusion." In this case series study, 34 patients had before and after ECP myocardial perfusion using symptom-limited, quantitative SPECT imaging. While post ECP angina class decreased from 2.7 to 1.7 (p < 0.001) and exercise duration increased 1 minute (p = 0.03), there was no difference in myocardial perfusion, which seems to contradict earlier case series studies (Tartaglia, Stenerson et al. 2003; Urano, Ikeda et al. 2001; Stys, Lawson et al. 2002; Bagger, Hall et al. 2004; Springer, Fife et al. 2001). This small study that focuses on theoretical physiologic mechanisms provides little information on clinical effectiveness of treatment.
- Soran 2006 (17), a recent publication, is mentioned. In this study, IEPR data are used for a two-year cohort study which included 363 refractory angina patients with a left ventricular ejection fraction $\leq$ 35%, as assessed by either echocardiography, ventriculography, or gated blood pool scan, with no time given as to when the study was performed. The stated purpose of this study was to describe the 2-year follow-up of patients with refractory angina who were treated with ECP therapy, and also were identified in the IEPR database as having had severe LV dysfunction (suggesting the diagnosis of heart failure). Only patient data from sites with $\geq$ 85% complete follow-up were included, thus eliminating patients who did not meet this criterion. Immediately post ECP therapy, 77% of the patients improved more than one angina class, and 18% had no angina. At two years, only 265 patients (73%) completed follow up and 55% of the patients had sustained improvement in angina class. Quality of life measures using a Likert scale indicated that 58% of patients had improved quality of life compared to baseline, and at 2 years follow-up, 63% had improved compared to baseline. As the authors note, "A primary limitation of this study is the lack of a control group to assess outcomes," and they recommend a more rigorous evaluation of the effect of EECP on these outcomes with a randomized clinical trial. The IEPR registry was designed for outcomes for angina patients, and gives little evidence for treatment effects for heart failure (Blue Cross Blue Shield, 2006).
- A recently published article by Lawson 2006 (37) is presented as evidence that CCSC II angina should be covered. Lawson included 112 patients with Class II angina and 1,345 patients with Class III or IV angina at entry from the IEPR. It is not clear how these particular patients were selected from the > 5,000 patients in the IEPR, or whether they differed from patients who were not in the registry. Thus, selection bias is likely in the study patients. Additionally, this study is very similar to a previously published study, Michaels 2004. We were unable to determine how many patients have been reported multiple times in these registry reports. Sixty-one percent of the Class II group had improvement of at least one angina class compared with 78% of 1,345 patients with Class III or IV angina at immediate post ECP follow-up. At 2 year follow-up, 70% in Class II vs. 81% in Class III/IV had an improvement by at least one CCSC angina class. There was a decrease in the number of angina episodes per week and reduction in sublingual nitroglycerin use per week in both groups immediately following (p < 0.001) and at two years post EECP (p<0.001) compared to baseline, though it is not clear if outcomes were reported uniformly or systematically. Quality of life improved in 60% of Class II and 52% of Class III/IV immediately post-EECP therapy, and improvement was maintained at 2-year follow-up in 44% of Class II patients and 51% of Class III/IV patients, though it is unclear how quality of life was measured. Due to the limitations noted above, the subjective outcomes and manner of reporting, this study provides little new information.
- Stys 2001 (9), Michaels 2004 (16), Soran 2002 (18), Weisfogel 1980 (20), Fitzgerald 2003 (36), Amsterdam 1980 (29) have been cited in this decision memorandum, and the commenters provided no information that disagreed with our interpretation of these articles.

Other:

- Bonetti 2003 (15) and Barsness 2001(13) are review articles with no new information.

- Unpublished subgroup data from the 1999 MUST-EECP trial are presented as evidence for coverage of CCSC II angina. Little weight is given to limited data from unpublished subgroup analysis.
- Appendix C of Vasomedical's comment is presented as evidence that "Endpoints used in studies of EECP therapy adequately demonstrate improvement in measures of morbidity as well as symptom status and quality of life, supporting the conclusion of health benefits from the therapy." The choice of a study result simply considered in isolation from its other aspects does not alone support the conclusion of health benefits. Trial design, appropriate endpoint selection in the context of the study, appropriate statistical tools and valid and reproducible results for clinically meaningful outcomes are important to support the conclusion of health benefits from a specific therapy. Regardless of endpoint, if the study has no control then it is impossible to determine if any improvement is due to one aspect of therapy, as is the situation with the bulk of ECP published studies.
- Comments were made about the interpretation of Vijayaraghaven 2005(24). Table VI on page 151 shows the average number of all-cause hospitalizations by New York Heart Association (NYHA) Class, contrary to CMS stating the incidence of hospitalization was not shown by NYHA. CMS notes that the CHF class in Table VI has as the first column D/S ratio, the main grouping. The next column is NYHA Class for each D/S ratio. Total NYHA CHF Class as three groups is not presented, nor can the numbers as presented be combined to give an accurate estimate. Secondly, differences are noted in the number of patients in Table V reported for all-cause hospital admissions and the number of patients in Table III reported for LVEFs and Table IV NYHA CHF Class. All-cause hospitalizations were reported that included 7 terminal hospitalizations, whereas the data on LVEFs and NYHA CHF Class were reported on only the survivors. It is stated, "we felt presenting the data, as we did, better reflected the actual incidence of hospitalization resulting from ECP under our Graduated Pressure Regimen." CMS notes that the comparisons are before ECP and year after ECP for LVEF and NYHA class for surviving patients, where those who died are not included. For all-cause hospital admissions per patient, comparison is year before ECP and year after ECP. If a patient was very sick and had many hospitalizations before ECP, then died soon after ECP, this would appear to be a reduction in hospitalizations post treatment, a favorable outcome, even though the patient died.
- Several studies are cited where patients with CHF were adversely affected with standard pressure therapy (Lawson 2001 (26), Soran 2006 (17)), or where outcomes with older ECP devices produced conflicting results (Langou (27), Solignac (28)), with a conclusion that by comparison to graduated pressure, other therapies may be inferior. CMS contends that a difference in study results does not directly correlate to a difference in the devices; this would need to be shown by a comparative study of the devices.
- A comment was offered that, "The considerable concordance of data from the IEPR which has successfully collected data on 7500 of the approximately 45000 patients treated to date in the US, and two, positive, randomized controlled clinical trials for Angina(MUST-EECP) and Heart Failure (PEECH) create a considerable body of data proving the clinical efficacy of EECP therapy." From this it can be concluded that from the IEPR studies, only 17% of those in the US who have received treatment are included in this registry. Again, the possibility of substantial selection bias cannot be overlooked. What are the results for the other 83% who are not documented in the registry? This circumstance casts doubt on the generalizability of its findings.
- Additional articles or books were cited that were either unrelated to ECP treatment or not peer-reviewed.

One comment included this statement, "Treatment with EECP clearly fulfills the American College of Cardiology guideline for chronic stable angina that specifies that treatment should reduce the symptoms of angina and occurrence of ischemia, and does so in a cohort of patients with few other viable alternative therapies." Similarly, a comment suggested that ECP therapy should not be held to the standard of mortality reduction, "…while we understand the need for mortality data to describe the benefit of costly life-long drug and complex interventional therapies, we do not believe that it is relevant in the evaluation of EECP therapy." This same sentiment was also expressed by some in the general public comments, with reference to page 48 and 59 of the ACC chronic stable angina guideline. However, on review of the guideline, these citations refer to pharmacological therapy for stable angina and choice of outcomes, rather than to ECP. ECP is discussed in the ACC guideline under, "Recommendations for Alternative Therapies for Chronic Stable Angina in Patients Refractory to Medical Therapy Who are not Candidates for Percutaneous Intervention or Surgical Revascularization." Under the ECP heading it is further mentioned, "However, additional clinical trial data are necessary before this technology can be recommended definitively," as is previously mentioned in the evidence section of this decision memorandum.

Additional comments with evidence:

Two letters were sent by physicians to the American College of Cardiology requesting their support. The referenced studies in these letters have either been reviewed in the evidence section of this memorandum, are discussed above, or lack direct relevance to the issue under consideration. Also included are two articles published only in proceedings without peer-review, and 78 published abstracts, many of which appeared to overlap published articles. Much less weight can be given to proceedings and abstracts.

D. Comments without Evidence

CMS received one hundred and four comments from physician and non-physician providers of ECP, (44 physician, 60 non-physician), with all comments being supportive of ECP. About 10 percent of total commentors indicated support for expansion to both class II angina and congestive heart failure, but there was an equal percentage that only supported expansion for congestive heart failure. A few supported expansion for only angina, and only 2 supported expansion for acute myocardial infarction and 1 supported expansion for cardiogenic shock. There were numerous comments that were positive but did not indicate support for the specific expansion of coverage while others suggested coverage for all heart patients, or anyone. Some suggested use as a preventive treatment, or offering this therapy to patients once a year to prolong life. This statement reflects a common sentiment, "Patients do better the sooner they get in for treatments before all major arteries are so clogged up even EECP does not have that much impact on their health," though there is no evidence to suggest that ECP is preventive therapy.

The majority of comments were by way of a form letter or some variation of a form letter. Overall, comments from patients reported improvement with their pain and ability to perform activities. Many commented on the "remarkable" or "extreme" improvements with ECP therapy, with comments such as, "God gave man the ability to grow collateral vessels and capillaries. EECP merely harnesses this God-given ability. A surgeon can-not do this. A drug cannot do this." And similarly, "I believe it to be a miracle." Providers commented, "You not only improve or stop their angina, the great side effects from this treatment tremendously improve our patients quality of life. Just a few are, improve or stop having SOB, improved exercise tolerance (patient can split & stack wood with diagnosis of angina & CHF after receiving 35 treatments), lowers blood pressure (some have had meds reduced or stopped), improved kidney functions, better vision, can sleep better at nite, improve speech in a patient who, had also had a CVA, helped ED [erectile dysfunction], hair growth & one 86 y/o patient resumed driving after 1 ½ years." Another commenter included improvement in diabetes, glaucoma, macular degeneration, and COPD. One commenter referred to the benefit as, "Lazarus like recoveries." The expression of these personal observations and feelings is appreciated but can be influenced by many different variables, so it is difficult to sort out the possible benefits from the device. The clinical evidence does not suggest such dramatic benefits.

As is said in one of the public comments, "this therapy provides the opportunity for extensive education of our patients regarding their medications, diet, signs and symptoms of angina/heart failure. As the patient begins to understand their own individual response to their plan of care, they feel empowered to handle their chronic conditions." Another commentor noted, "… the close surveillance by capable eecp trained nurses." It is very difficult to judge how much the effect of this care contributes to health benefits the patient may experience and how much of the effect is from the ECP therapy.

Some commentors wanted approval of ECP for CHF patients with an EF less than 35% who have ischemic cardiomyopathy with demonstrable areas of reversible ischemia by stress test. In January 2006 the manufacturer provided limited subgroup data from the PEECH trial to support this comment. This group of patients had not been identified a priori as the group of heart failure patients that should be targeted for ECP therapy. The unpublished evidence that was presented is insufficient to determine if this select group of heart failure patients would benefit from ECP therapy, particularly given the overall results of the PEECH trial.

While public comments from providers and patients describing their personal experiences are informative, our NCDs rely on published scientific evidence in making coverage determinations. It is our experience that procedures, therapies, etc., gain widespread support in the medical community as the published, scientific evidence convinces providers and the representative societies of the value they offer.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under Title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member." § 1862(a)(1)(A). This section presents the agency's evaluation of the evidence considered and conclusions reached for the assessment questions.

CMS focused on this general question for the listed indications:

Is the evidence sufficient to conclude that as a result of treatment with external counterpulsation the Medicare population will have health benefits for the following conditions?

- Canadian Cardiovascular Society Classification (CCSC) II angina

- Heart Failure - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 35%
  - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 40%
  - New York Heart Association Class IV heart failure
  - Acute heart failure
- Cardiogenic shock
- Acute myocardial infarction

General Issues

Study design is important for convincing and dependable outcome results. Case series do not provide evidence about whether the treatment itself directly causes the subsequent outcome, or whether some other concurrent factor is responsible for the observed outcome (or, to what extent each factor contributes, if any contribution is made, to the outcome). The type of study that reports what is observed, without a comparative control group, deserves less weight than those studies that do have a comparison group because all the potential events that can occur during treatment, including those caused by additional therapies, can not be separated from the overall effect. Because of this study design, one is left with uncertainty about which factor of the many that go into the complex interaction of patient, treatment and disease, produced the reported result. Placebo effect is a consideration, therefore convincing and dependable outcome results are needed to dispel this possibility. Factors that reliably affect morbidity and mortality are outcome results of interest to CMS. When study outcomes of uncertain clinical significance are chosen by investigators in the design of a study, those outcomes are rarely useful in making a determination of reasonable and necessary.

In the technology assessment conducted by Blue Cross Blue Shield Association Technology Evaluation Center, ECP therapy was evaluated for chronic stable angina and for chronic heart failure and met only one TEC criteria; FDA approval. The following TEC criteria were not met: 1) the scientific evidence must permit conclusions concerning the effect of the technology on health outcomes; 2) the technology must improve net health outcomes; 3) the technology must be as beneficial as any established alternatives; 4) the improvement must be attainable outside the investigational settings" Additionally, they state, "At this time, it would also be considered harmful to promote the use of a less-invasive, but less-proven technology over currently available, life-saving, but invasive technology, such as revascularization." The ACC/AHA guideline did not recommend ECP for chronic heart failure and assigned the lowest level of evidence to ECP therapy for angina, which suggests potential benefit that requires further clinical trial data before a definite recommendation. Importantly, the ACC supported the CMS proposed decision.

Is the evidence sufficient to conclude that as a result of treatment with external counterpulsation therapy the Medicare population will have health benefits for stable angina?

Most of the published studies are of patients with stable angina. No separate studies on Class II angina have been published. An ad-hoc subgroup analysis has been presented as evidence. Examining the evidence for stable angina, most of the available published evidence is limited by lack of a comparison group. It is difficult to rely on observational evidence when there is no comparison group to say that one specific treatment is effective when there are many concurrent changes. Therefore, much of the best evidence rests on the MUST-EECP trial. This trial had many exclusion criteria, which limit the generalizability of the results to other patients. In this study, there was a significant drop-out rate, with a lack of detail as to why the patient dropped out. Those patients were not included in the analysis. Given the high drop-out rate, it is unclear if those who were having a poor response were the ones that dropped out, thus producing bias. When intention to treat analysis is applied, only 56 patients out of 71 randomized were analyzed. Intention to treat analysis is a strategy for analyzing data from a randomized controlled trial. All participants are included in the group to which they were allocated, whether or not they received or completed the treatment given to that group. When participants are excluded, the premise of an equal baseline between the two groups is disrupted, and the validity of the evidence is lessened. There is uncertainty regarding the clinical significance of the reported improvement in physiologic measures. While exercise capacity (maximal oxygen uptake for a given workload, expressed in metabolic equivalents) has been shown to be an independent predictor of risk of death and cardiac events among asymptomatic women and men, the clinical benefit of a 49 second increase in time to ST-segment depression is unclear in those with chronic angina. Thus, a surrogate outcome such as this is difficult to assess in determining reasonable and necessary. The rationale for method of analysis is not always clear. For instance, what is the clinical significance when assessment by mean angina counts is not statistically significant, but an analysis using categories of percentage improvement shows statistical significance? Is the point of statistical significance the primary interest? The other two measures, nitroglycerin usage and exercise duration, showed no difference between groups. While ECP has been described as safe, in the randomized study, 55% of the ECP patients had adverse experiences as compared to 26% in the sham treatment group.

The subsequent quality of life study included only 54% of the original participants. It is not clear how these patients differed from the rest of the original group, again introducing selection bias. How would the results change if all of the original patients were included? Questionnaire score changes are presented without baseline scores, creating difficulty in interpretation for the reader. Other limitations include small sample size (low power to detect differences), quality of life data not being correlated with the previous data from exercise testing, anginal symptoms, or the anginal episodes for the one year outcome. When results such as this are not presented, one is left wondering if those that showed improvement in other measures in the MUST-EECP trial may not have shown an improvement in quality of life. It is unclear why this correlation was not done.

The remainder of the studies are small case series and reports of registry data. For both types of studies, there is no comparison group, so it is difficult to determine if improvement is due to ECP. Though the results appear positive, the method of data collection (where there is no comparison group and it is unclear what patients were excluded) bias these results. Some articles suggest that the placebo effect may be important. It has been reported that the use of medical devices may be associated with an enhanced placebo effect (Bonetti, Gadasalli et al. 2004). While the placebo effect remains enigmatic, it can be robust, and angina is known to have a high placebo response (Rana, Mannam et al. 2005). In a study population of patients with coronary heart disease, placebo effects were found to have longevity (Rana, Mannam et al. 2005). This effect is not limited to symptomatic endpoints, but also to end points such as exercise time and magnetic resonance imaging, though it is not clear why this happens. Having a benefit over time does not rule out the placebo effect, as the benefits of placebo therapy on coronary heart disease have been shown to persist for at least as long as 2 years (Rana, Mannam et al. 2005). Another important registry issue is that follow-up is done by phone based on the patient's self report, and is subject to recall bias.

General effects not specific to angina may also be important with ECP therapy and cannot be excluded given the existing literature. Close medical attention is provided at specific centers, with prolonged duration of treatment, which may have a significant effect in reducing the symptoms of treated patients through various mechanisms. These factors may include better patient compliance with drug treatment regimes, closer adherence to treatment guidelines among treating physicians, accompanying patient education on lifestyle modification, diet, medications, and physical activity, as well as motivated patients.

While the hemodynamic effects of ECP are dependent on the magnitude of applied external pressure, symptoms in patients with angina improved even in the absence of an optimal hemodynamic effect, which also suggests that nonspecific effects may contribute to the symptomatic benefit of ECP (Suresh, Simandl et al. 1998; Stys, Lawson et al. 2001; Bonetti, Holmes et al 2003). Additionally, if hemodynamics are important it is not intuitive that when the DA ratio falls rather than increases, an improvement is shown. From this, it would appear that DA ratio does not have an effect on symptoms. While ECP has been found to cause acute changes in hemodynamics, there have been no studies of chronic changes in hemodynamics following ECP. Importantly, hemodynamic measurements do not take the place of accepted measures, such as angiography, for cardiovascular disease.

In case series studies (including registry data), morbidity and mortality data without a comparable study comparison is difficult to evaluate. Comparison between studies with different selection criteria and indications, data quality and completeness, and historical point in time is problematic at best for comparison of a treatment benefit estimate between the two groups. Narrowly focused morbidity reporting may miss important treatment related effects.

An issue related to the possibility of a training effect on skeletal muscle made possible by a placebo effect on chest pain leads to a similar exercise-related question particularly in Class II angina patients – those who have angina only with strenuous exercise. ECP has been reported to have effects similar to physical training (Bonetti, Holmes et al. 2003; Sinvhal, Gowda et al. 2003; Guerci 2000). It is not clear how the effects of ECP are different from exercise in patients who can participate in physical conditioning. In other words, will an exercise program of walking achieve similar results?

In summary, the evidence was not adequate to support a health benefit for treatment of Canadian Cardiovascular Society Classification II angina with external counterpulsation therapy.

Is the evidence sufficient to conclude that as a result of treatment with external counterpulsation therapy the Medicare population will have health benefits for heart failure?

Published evidence on the use of ECP therapy to treat heart failure includes data from a small case series feasibility study (between 19 and 24 patients) and data from a registry (about 1,385 patients with a history of heart failure or EF $\leq$ 35% who completed ECP therapy), which is used to track acute and long-term outcome for consecutive patients treated for chronic angina. Although we reviewed unpublished data, less weight is given to this evidence. As with the same registry data for stable angina, there are significant methodological problems, such as suggesting direct risk comparison between different studies and no clear statement of adjustment for comorbidities or treatment changes. Additionally, it is not clear if those who are not included in the results differ from those who are excluded. Though the results of these case series studies again appear positive, the method of data collection limits any reliable conclusions. One device firm suggests that standard therapy pressures (e.g. up to 300 mm Hg) are appropriate treatment for congestive heart failure, while another device firm claims that higher pressures are harmful in CHF, suggesting that graduated lower pressures are the appropriate therapy. These two ideas would appear mutually exclusive. A comparison trial would best address this question.

In summary, the evidence was not adequate to support a health benefit for treatment of heart failure with external counterpulsation therapy.

Is the evidence sufficient to conclude that as a result of treatment with external counterpulsation therapy the Medicare population will have health benefits for cardiogenic shock?

Cardiogenic shock is a life-threatening hemodynamically unstable state. The body of evidence to support the use of ECP for this indication consists of a small case series from 1974 and also two more current small case series in hemodynamically stable patients, not in patients who have a life-threatening hemodynamically unstable state. The results of these studies may suggest that ECP is comparable to IABP treatment in certain limited circumstances, but not for the current treatment of cardiogenic shock. A study comparing prevailing therapies in hemodynamically unstable patients has not been presented as evidence.

In summary, the evidence was not adequate to support a health benefit for treatment of cardiogenic shock with external counterpulsation therapy.
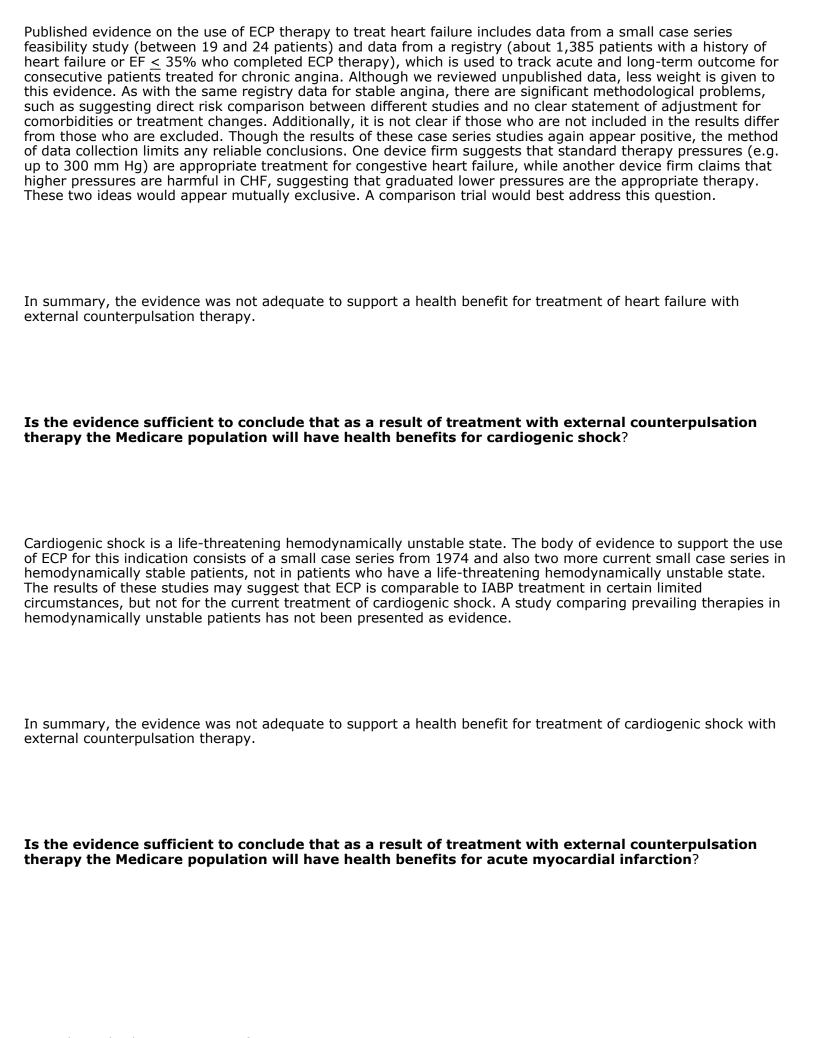
Is the evidence sufficient to conclude that as a result of treatment with external counterpulsation therapy the Medicare population will have health benefits for acute myocardial infarction?

Much has changed in both the definition and the care of this illness since the study using ECP therapy was published in 1980 (Joint ESC/ACC Committee 2000). Patients who in 1980 met the criteria for acute MI may not meet the current diagnostic criteria. The standard of care for acute MI has changed since 1980, so it is doubtful that clinicians would apply the same manner of therapy as they did in 1980. Though the 1980 study results may suggest that ECP treatment may have positively impacted morbidity and mortality in acute myocardial infarction, results of this study are not relevant considering the current standard of care.

Thus, we do not believe that there is adequate evidence to support a health benefit for treatment of acute myocardial infarction with the external counterpulsation therapy.

Conclusions

While there have been many articles published on the topic of ECP, the contemporary data consists of one published randomized controlled trial (139 enrolled), an unpublished randomized controlled trial, nonrandomized small case series studies, various analyses of the > 5,000 patients entered into the EECP registry, and one study of the Cardiomedics registry. The accumulated data do support the current usage in those who are not amenable to surgical intervention, but does not support the expansion of coverage. Observational studies can assess the strengths and weaknesses of the treatment under study, but cannot test the key hypotheses.

IX. Decision

The Centers for Medicare and Medicaid Services (CMS) has determined that the evidence is not adequate to conclude that external counterpulsation therapy is reasonable and necessary for the treatment of:

- Canadian Cardiovascular Society Classification (CCSC) II angina
- Heart Failure - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 35%
  - New York Heart Association Class II/III stable heart failure symptoms with an ejection fraction of $\leq$ 40%
  - New York Heart Association Class IV heart failure
  - Acute heart failure
- Cardiogenic shock
- Acute myocardial infarction

Current coverage as described in Section 20.20 of the NCD manual will remain in effect.

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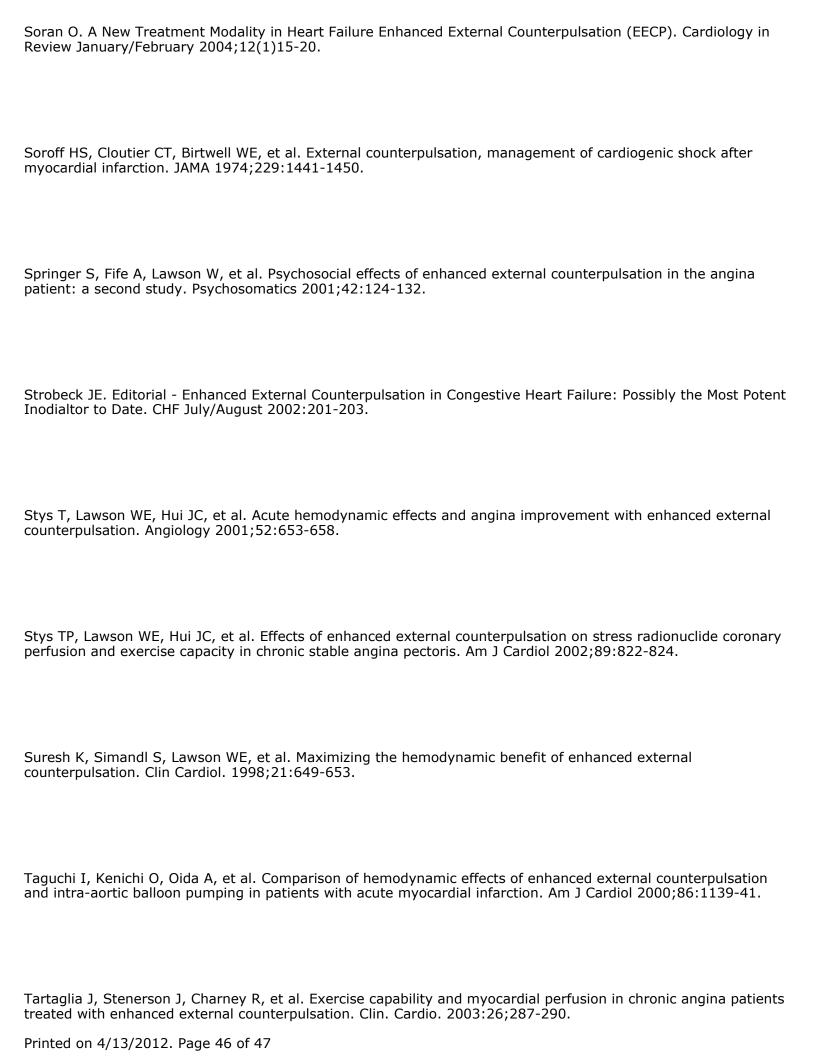Ryan TJ, Anderson JL, Antman EM, et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force of Practice Guidelines (Committee on Management of Acute Myocardial Infarction). J AM Coll Cardiol 1996; 28:1328-1428.

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